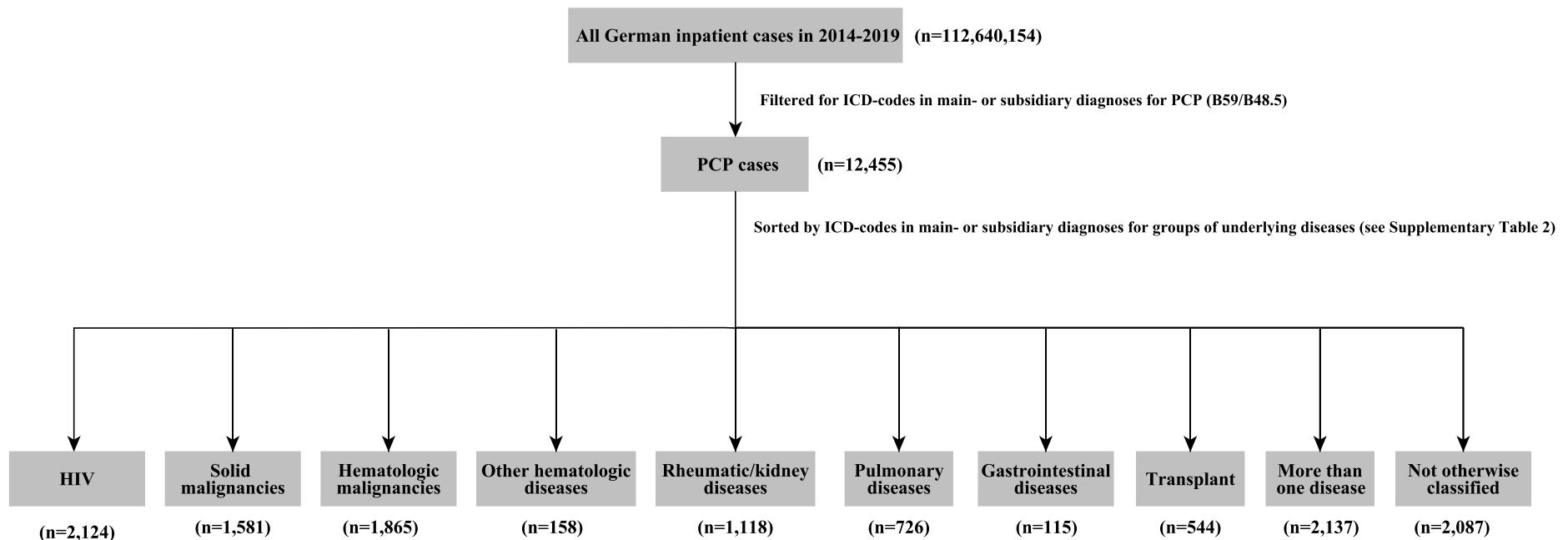


**Supplementary Appendix to *Evolving Epidemiology of Pneumocystis Pneumonia: Findings from a Longitudinal Population-Based Study and a Retrospective Multi-Center Study in Germany***

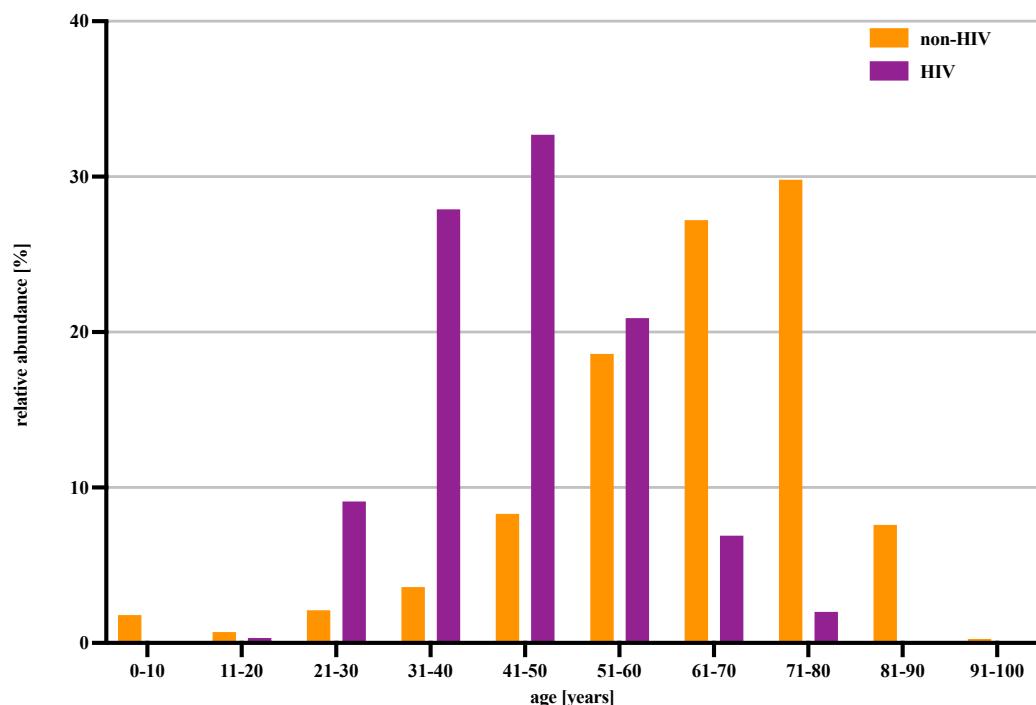
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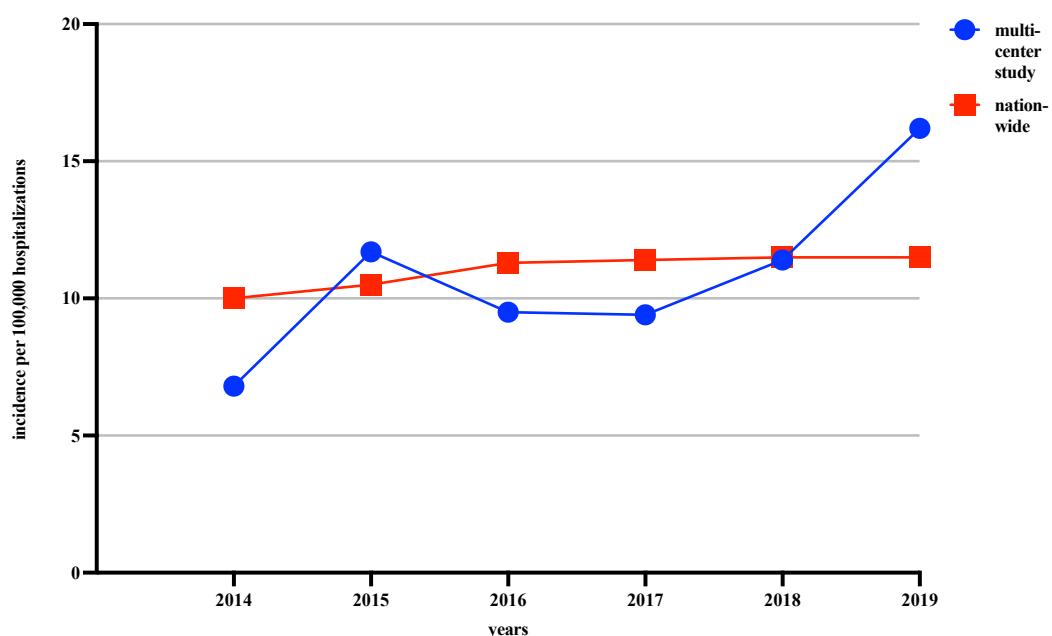
**Supplementary Figure 1. Analytic algorithm for identification of PCP cases and risk factors in the nationwide secondary data**

For technical reasons, this algorithm had to be applied to each year under consideration separately. Indicated patient numbers represent the total sum of all patients from 2014 to 2019.



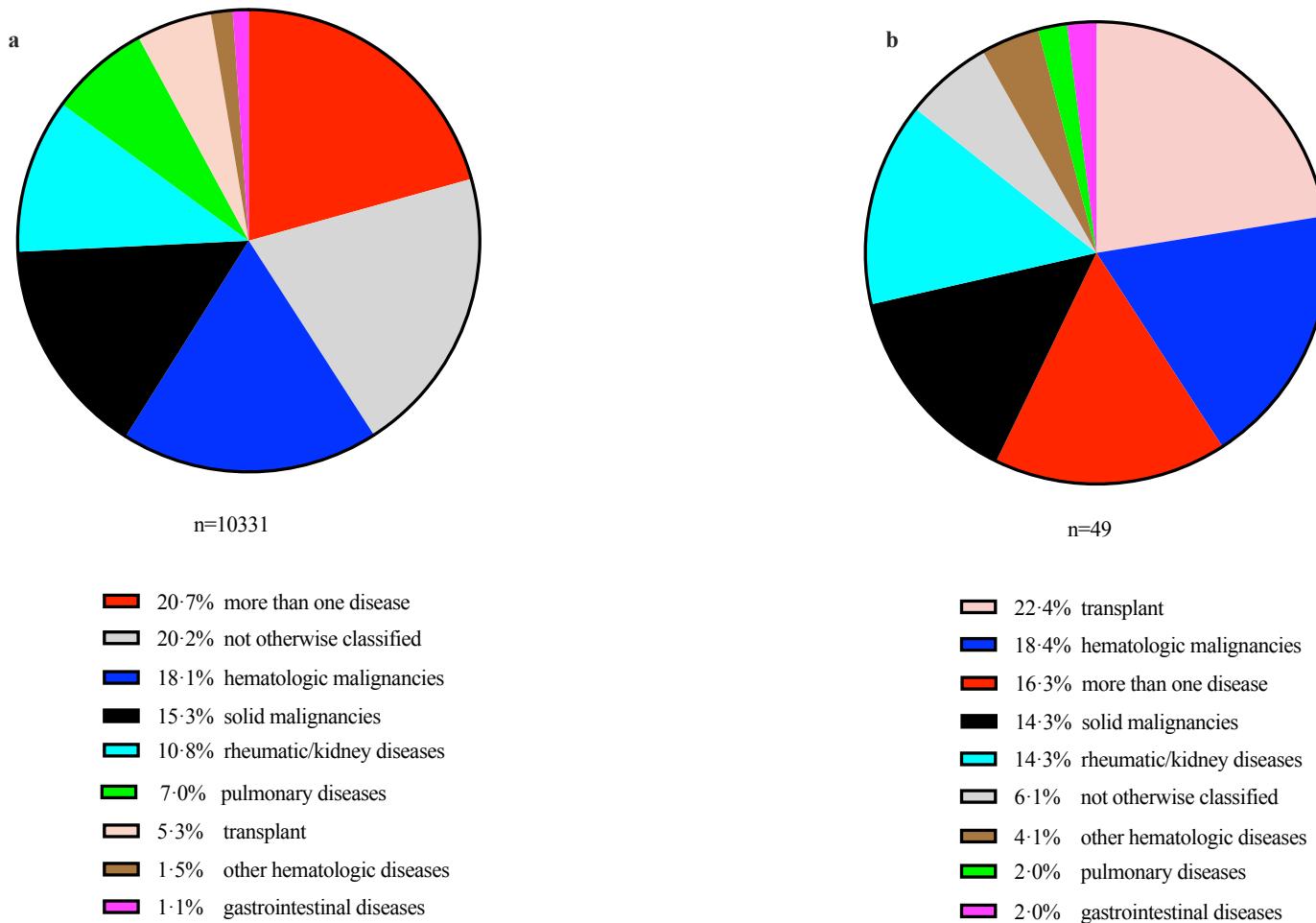
**Supplementary Figure 2. Age distribution of HIV and non-HIV PCP patients in Germany**

Relative abundance of HIV and non-HIV PCP patients across age groups is shown. PCP patients were identified from the DRG statistics of the German Federal Statistical Office from 2014 to 2019. For both groups, the percentages sum up to 100 each. This graph does not reflect the difference in absolute numbers between the HIV and non-HIV group (2,124 HIV vs. 10,331 non-HIV patients, respectively).



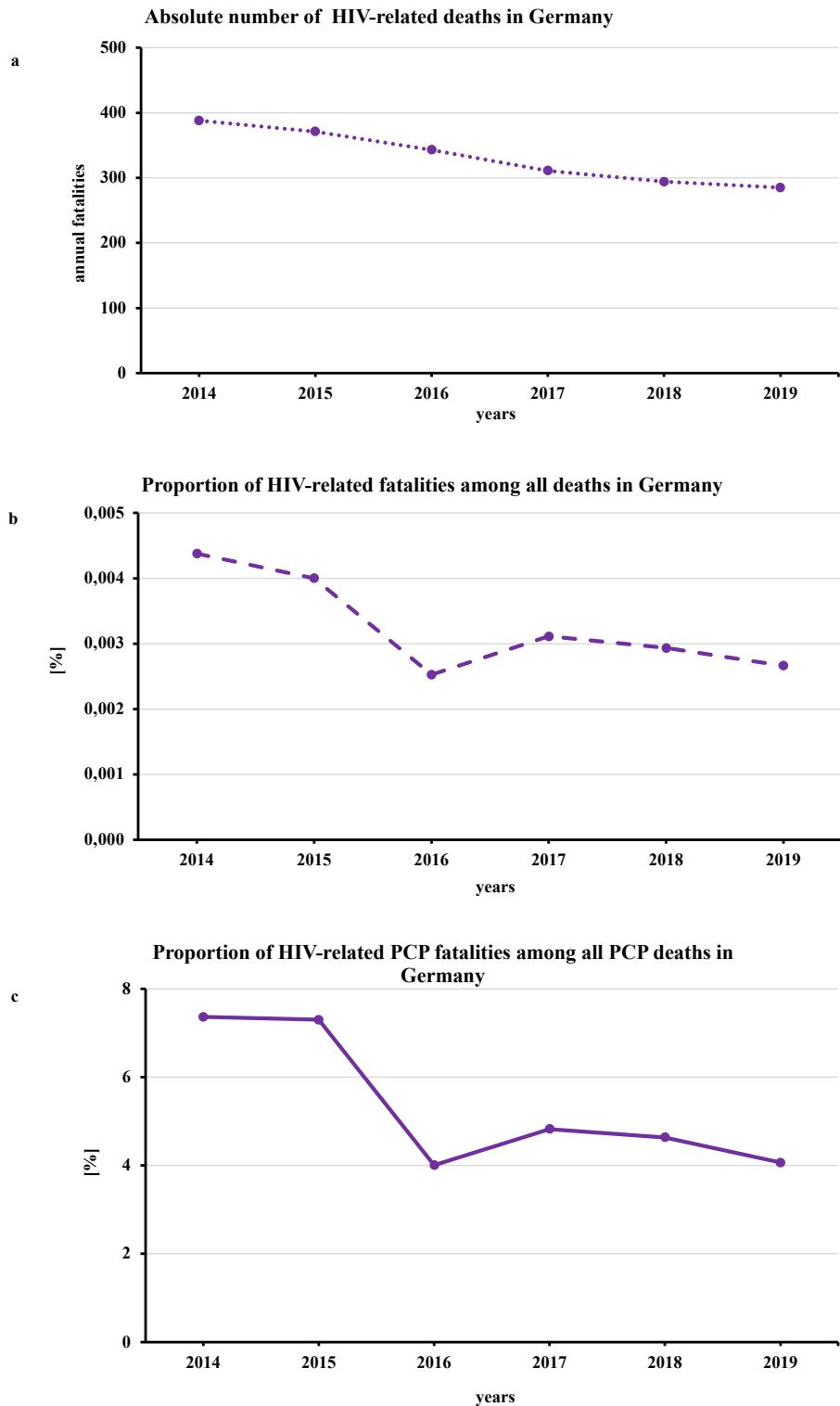
**Supplementary Figure 3. PCP incidence multi-center study vs. nationwide**

The graph shows the incidence of PCP cases per 100,000 hospitalizations in our multi-center study (blue) and the secondary data analysis of all German inpatient cases (red) from 2014 to 2019. Averaged over the entire observation period, the incidence was 10·5 in the multi-center study and 11·1 per 100,000 hospitalizations in the nationwide analysis.



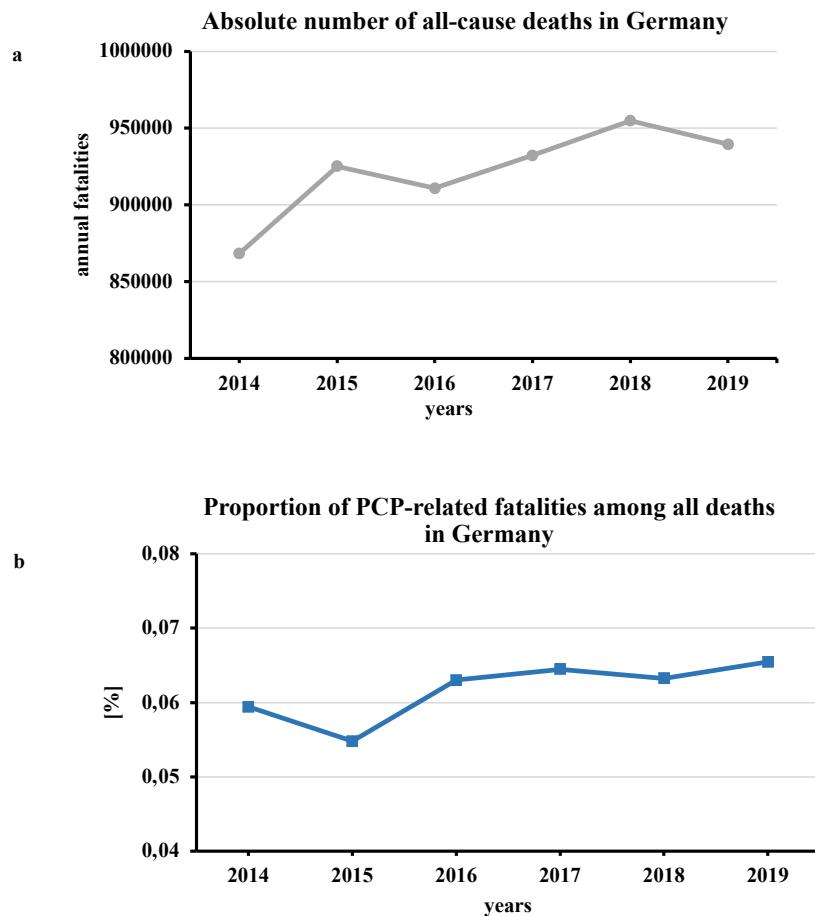
**Supplementary Figure 4. Underlying diseases other than HIV of PCP in the multi-center study vs. nationwide**

Pie charts depict the distribution of underlying diseases and conditions for the development of PCP among the non-HIV group in the nationwide secondary data analysis (a) and the concomitant multi-center study (b). Noteworthy is an overrepresentation of the group "transplant" in the multi-center study. This is most likely due to the fact that the clinics under investigation here are transplantation centers that treat a significantly larger number of organ transplant recipients than most German hospitals. Reasons for the clear predominance of the "not otherwise classified" group in the nationwide secondary data analysis are elaborated on in the "discussion" section.



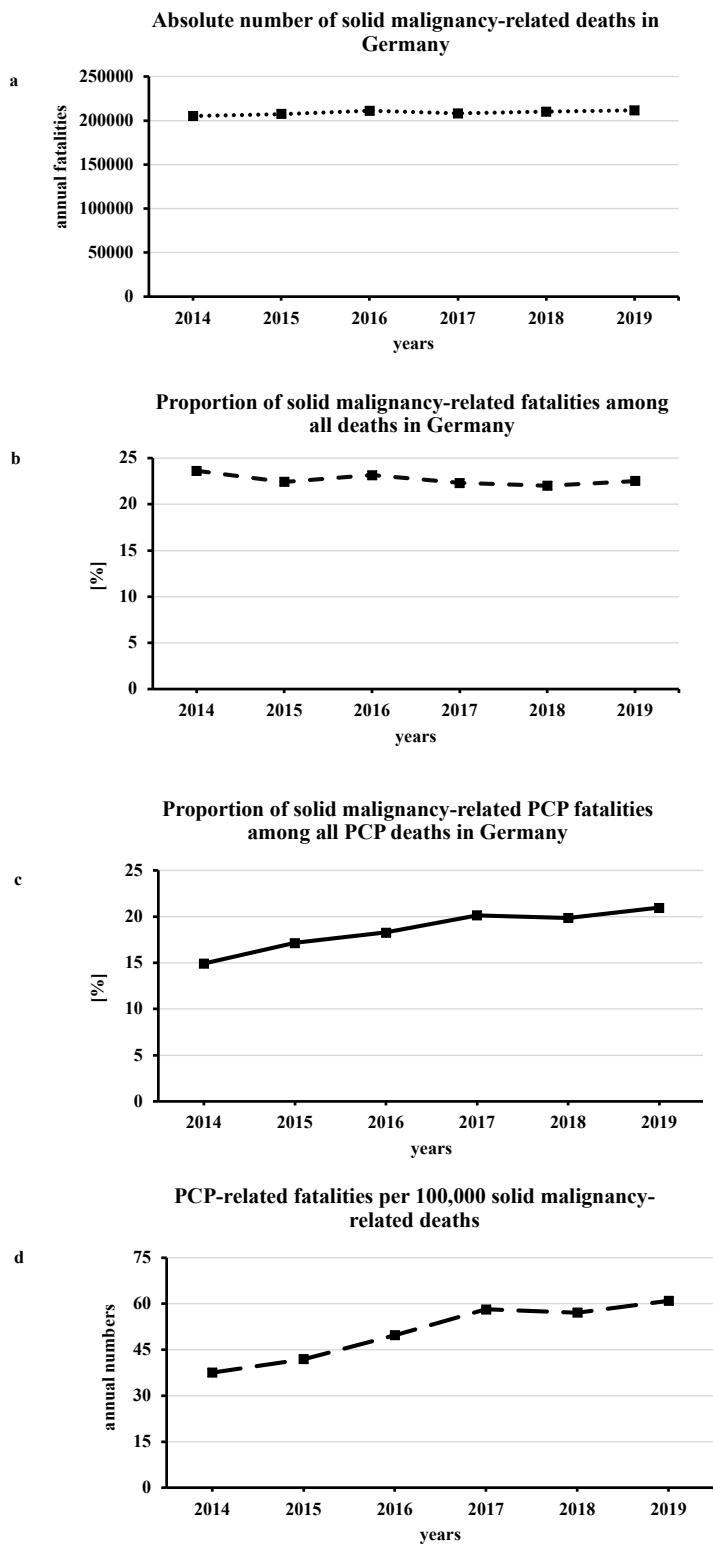
**Supplementary Figure 5. HIV related deaths in Germany 2014 to 2019**

(a) The number of HIV-related fatalities in Germany decreased by 26·5% from 2014 to 2019. This was accompanied by a decrease in the proportion of HIV-related deaths among all deaths in Germany (b).<sup>1</sup> The decline in absolute and relative death rates was also reflected in the proportion of HIV-related PCP deaths among all PCP-related deaths (c).



**Supplementary Figure 6. Proportion of PCP-related deaths in all fatalities in Germany 2014 to 2019**

- (a) The number of all-cause deaths in Germany increased from 868,356 to 939,520 between 2014 and 2019.<sup>1</sup>
- (b) The proportion of PCP-related deaths herein nevertheless increased by 9·2% (from 59 in 100,000 deaths to 65 in 100,000 deaths).



**Supplementary Figure 7. Development of solid malignancy-related deaths and proportion of PCP-related deaths therein from 2014 to 2019**

(a) The number of deaths caused by solid malignancies in Germany increased slightly from 2014 to 2019 (205,149 to 211,601), (b) and the proportion of these among all deaths decreased slightly (23.6% to 22.5%).<sup>1</sup> (c) At the same time, the proportion of solid malignancy-related PCP fatalities among all PCP-related deaths in Germany increased sharply (14.9% to 23.0%), (d) as well as the number of PCP-related fatalities per 100,000 solid malignancy-related deaths (37.5 to 61.0 per 100,000 deaths).

**Supplementary Table 1. Diagnostic-, inpatient course-, and organ dysfunction codes**

<b>German Operation and Procedure Classification System key codes for diagnostic and therapeutic procedures</b>	
Tracheobronchoscopy and bronchial lavage	1-620 1-843
Thorax CT	3-202 3-222
Thorax MRI	3-809 3-822
Intensive care treatment	8-980 8-98d 8-98f
Mechanical ventilation	8-70 8-71 8-72
Renal replacement therapy	8-853 8-854 8-855 8-856 8-857
Palliative care treatment	8-982 8-98e 8-98h
Cardiopulmonary resuscitation	8-77
<b>ICD-10 codes for organ dysfunctions</b>	
Cardiovascular	I95.9: Hypotension, unspecified R57.9: Shock, unspecified R57.8: Other shock
Respiratory	J96: Respiratory failure, not elsewhere classified J96.9: Respiratory failure, unspecified J80: Acute respiratory distress syndrome J98.4: Other disorders of lung R06.0: Dyspnea R06.8: Other abnormalities of breathing
Central nervous system	F05: Delirium G93.1: Anoxic brain damage G93.4: Encephalopathy R40: Somnolence, stupor and coma
Renal	N17: Acute kidney failure N19: Unspecified kidney failure
Metabolic	E87.2: Acidosis
Hematologic	D65: Disseminated intravascular coagulation D68.8: Other specified coagulation defects D68.9: Coagulation defect, unspecified D69.5: Secondary thrombocytopenia D69.6: Thrombocytopenia, unspecified
Hepatic	K72.0: Acute and subacute hepatic failure K76.2: Central hemorrhagic necrosis of liver K72.7-!: Hepatic encephalopathy and hepatic coma K76.3: Infarction of liver
Multi-organ dysfunction	R65.1!: SIRS due to infection with organ dysfunction R57.2: Septic shock

CT, computed tomography; MRI, magnetic resonance imaging; SIRS, systemic inflammatory response syndrome

**Supplementary Table 2. ICD-10 codes for immunosuppressive conditions**

Underlying diseases	Corresponding ICD-10 codes
HIV	B20.- HIV disease resulting in infectious and parasitic diseases B21.- HIV disease resulting in malignant neoplasms B22.- HIV disease resulting in other specified diseases B23.- HIV disease resulting in other conditions B24.- Unspecified HIV disease
Solid malignancies	C00.- Malignant neoplasm of lip C01.- Malignant neoplasm of base of tongue C02.- Malignant neoplasm of other and unspecified parts of tongue C03.- Malignant neoplasm of gum C04.- Malignant neoplasm of floor of mouth C05.- Malignant neoplasm of palate C06.- Malignant neoplasm of other and unspecified parts of mouth C07.- Malignant neoplasm of parotid gland C08.- Malignant neoplasm of other and unspecified major salivary glands C09.- Malignant neoplasm of tonsil C10.- Malignant neoplasm of oropharynx C11.- Malignant neoplasm of nasopharynx C12.- Malignant neoplasm of piriform sinus C13.- Malignant neoplasm of hypopharynx C14.- Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx C15.- Malignant neoplasm of esophagus C16.- Malignant neoplasm of stomach C17.- Malignant neoplasm of small intestine C18.- Malignant neoplasm of colon C19.- Malignant neoplasm of rectosigmoid junction C20.- Malignant neoplasm of rectum C21.- Malignant neoplasm of anus and anal canal C22.- Malignant neoplasm of liver and intrahepatic bile ducts C23.- Malignant neoplasm of gallbladder C24.- Malignant neoplasm of other and unspecified parts of biliary tract C25.- Malignant neoplasm of pancreas C26.- Malignant neoplasm of other and ill-defined digestive organs C30.- Malignant neoplasm of nasal cavity and middle ear C31.- Malignant neoplasm of accessory sinuses C32.- Malignant neoplasm of larynx C33.- Malignant neoplasm of trachea C34.- Malignant neoplasm of bronchus and lung C37.- Malignant neoplasm of thymus C38.- Malignant neoplasm of heart, mediastinum and pleura C39.- Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs C40.- Malignant neoplasm of bone and articular cartilage of limbs C41.- Malignant neoplasm of bone and articular cartilage of other and unspecified sites C43.- Malignant neoplasm of skin C44.- Other malignant neoplasms of skin

	C45.- Mesothelioma C46.- Kaposi's sarcoma C47.- Malignant neoplasm of peripheral nerves and automatic nervous system C48.- Malignant neoplasm of retroperitoneum and peritoneum C49.- Malignant neoplasm of other connective and soft tissue C50.- Malignant neoplasm of breast C51.- Malignant neoplasm of vulva C52.- Malignant neoplasm of vagina C53.- Malignant neoplasm of cervix uteri C54.- Malignant neoplasm of corpus uteri C55.- Malignant neoplasm of uterus, part unspecified C56.- Malignant neoplasm of ovary C57.- Malignant neoplasm of other and unspecified female genital organs C58.- Malignant neoplasm of placenta C60.- Malignant neoplasm of penis C61.- Malignant neoplasm of prostate C62.- Malignant neoplasm of testis C63.- Malignant neoplasm of other and unspecified male genital organs C64.- Malignant neoplasm of kidney, except renal pelvis C65.- Malignant neoplasm of renal pelvis C66.- Malignant neoplasm of ureter C67.- Malignant neoplasm of bladder C68.- Malignant neoplasm of other and unspecified urinary organs C69.- Malignant neoplasm of eye and adnexa C70.- Malignant neoplasm of meninges C71.- Malignant neoplasm of brain C72.- Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system C73.- Malignant neoplasm of thyroid gland C74.- Malignant neoplasm of adrenal gland C75.- Malignant neoplasm of other endocrine glands and related structures
Hematologic malignancies	C81.- Hodgkin lymphoma C82.- Follicular lymphoma C83.- Non-follicular lymphoma C84.- Mature T/NK-cell lymphomas C85.- Other and unspecified types of non-Hodgkin lymphoma C86.- Other specified types of T/NK-cell lymphoma C88.- Malignant immunoproliferative diseases C90.- Multiple myeloma and malignant plasma cell neoplasms C91.- Lymphoid leukemia C92.- Myeloid leukemia C93.- Monocytic leukemia C94.- Other leukemias of specified cell type C95.- Leukemia of unspecified cell type C96.- Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue C97.- Malignant neoplasms of independent (primary) multiple sites D46.- Myelodysplastic syndromes

	D47.- Other neoplasms of uncertain or unknown behaviour of lymphoid, hematopoietic and related tissue Z94.81 Condition after hematopoietic stem cell transplantation with current immunosuppression
Other hematologic diseases	D59.- Acquired hemolytic anemia D60.- Acquired pure red cell aplasia D61.- Other aplastic anemias D76.- Other specified diseases with participation of lymphoreticular and reticuloohistiocytic tissue D80.- Immunodeficiency with predominantly antibody defects D81.- Combined immunodeficiencies D82.- Immunodeficiency associated with other major defects D83.- Common variable immunodeficiency D84.- Other immunodeficiencies
Rheumatic/kidney diseases	D86.- Sarcoidosis M30.- Polyarteritis nodosa and related conditions M31.- Other necrotizing vasculopathies M32.- Systemic lupus erythematosus M33.- Dermatopolymyositis M34.- Systemic sclerosis M35.- Other systemic involvement of connective tissue M05.- Seropositive rheumatoid arthritis M06.- Other rheumatoid arthritis M07.-* Psoriatic and enteropathic arthropathies M08.- Juvenile arthritis M09.-* Juvenile arthritis in diseases classified elsewhere M12.- Other specific arthropathies M13.- Other arthritis M14.-* Arthropathies in other diseases classified elsewhere M45.- Ankylosing spondylitis N00.- Acute nephritic syndrome N01.- Rapidly progressive nephritic syndrome N03.- Chronic nephritic syndrome N04.- Nephrotic syndrome L10.- Pemphigus L12.- Pemphigoid L13.- Other bullous disorders L14.-* Bullous disorders in diseases classified elsewhere
Pulmonary diseases	J43.- Emphysema J44.- Other chronic obstructive pulmonary disease J45.- Asthma J60.- Coalworker's pneumoconiosis J61.- Pneumoconiosis due to asbestos and other mineral fibers J62.- Pneumoconiosis due to dust containing silica J63.- Pneumoconiosis due to other organic dusts J64.- Unspecified pneumoconiosis J65.- Pneumoconiosis associated with tuberculosis J66.- Airway disease due to specific organic dust J67.- Hypersensitivity pneumonitis due to organic dust J68.- Respiratory conditions due to inhalation of chemicals, gases, fumes and vapors J69.- Pneumonitis due to solids and liquids J70.- Respiratory conditions due to other external agents

	E84.- Cystic fibrosis
Gastrointestinal diseases	K50.- Crohn disease (regional enteritis) K51.- Ulcerative colitis K75.4.- Autoimmune hepatitis
Transplant	Z94.0.- Kidney transplant status Z94.1.- Heart transplant status Z94.2.- Lung transplant status Z94.3.- Heart and lungs transplant status Z94.4.- Liver transplant status

HIV, human immunodeficiency virus; NK, natural killer cell

**Supplementary Table 3. Changes in PCP cases and deaths from 2014 to 2019**

Year	2014	2019	p-value (Chi-square test)
PCP cases	1,857	2,172	<0·0001
PCP deaths	516	615	0·0111

PCP, pneumocystis pneumonia

For the test of statistical significance, the population data provided by the German Federal Statistical Office as of December, 31 of the respective years were used (81,197,537 people in 2014 and 83,166,711 people in 2019).<sup>1</sup>

**Supplementary Table 4. Changes in PCP cases among different risk groups from 2014 to 2019**

Underlying diseases	Case number 2014	Case number 2019	Relative change (%)	p-value (Fisher's exact test)
HIV	346	331	-4·3%	0·0046
Solid malignancies	203	316	55·7%	0·0007
Hematologic malignancies	326	270	-17·2%	<0·0001
Other hematologic diseases	28	29	3·6%	0·6890
Rheumatic/kidney diseases	170	201	18·2%	0·9564
Pulmonary diseases	95	167	75·8%	0·0010
Gastrointestinal diseases	11	19	72·7%	0·3596
Transplant	76	67	-11·8%	0·0880
More than one disease	337	373	10·7%	0·4308
Not otherwise classified	265	399	50·6%	0·0005

PCP, pneumocystis pneumonia; HIV, human immunodeficiency virus

**Supplementary Table 5. Changes in PCP-related deaths among different risk groups from 2014 to 2019**

Underlying diseases	PCP-related deaths 2014	PCP-related deaths 2019	Relative change (%)	p-value (Fisher's exact test)
HIV	38	25	-34·2%	0·0188
Solid malignancies	77	129	67·5%	0·0086
Hematologic malignancies	117	88	-24·8%	0·0003
Other hematologic diseases	7	6	-14·3%	0·5860
Rheumatic/kidney diseases	41	58	41·5%	0·3996
Pulmonary diseases	26	36	38·5%	0·6010
Gastrointestinal diseases	4	5	25%	>0·9999
Transplant	18	17	-5·6%	0·4958
More than one disease	95	115	21·1%	0·9389
Not otherwise classified	93	136	46·2%	0·1021

PCP, pneumocystis pneumonia; HIV, human immunodeficiency virus

**Supplementary Table 6. Diagnostic procedures performed on PCP patients for each respective year (nationwide)**

Year	Procedure	HIV	Non-HIV	p-value HIV vs. non-HIV (Chi-square test)
2014	Thorax CT/MRI	202/346 (58·4 %)	1,091/1,511 (72·2 %)	<0·0001
	Bronchoscopy	239/346 (69·1 %)	1,089/1,511 (72·1 %)	0·2653
	Thorax CT/MRI <u>and</u> bronchoscopy	157/346 (45·4 %)	846/1,511 (56·0 %)	0·0004
2015	Thorax CT/MRI	241/399 (60·4 %)	1,143/1,568 (72·9 %)	<0·0001
	Bronchoscopy	267/399 (66·9 %)	1,129/1,568 (72·0 %)	0·0457
	Thorax CT/MRI <u>and</u> bronchoscopy	189/399 (47·4 %)	865/1,568 (55·2 %)	0·0053
2016	Thorax CT/MRI	215/356 (60·4 %)	1,308/1,785 (73·3 %)	<0·0001
	Bronchoscopy	231/356 (64·9 %)	1,281/1,785 (71·8 %)	0·0093
	Thorax CT/MRI <u>and</u> bronchoscopy	159/356 (44·7 %)	1,010/1,785 (56·6 %)	<0·0001
2017	Thorax CT/MRI	223/351 (63·5 %)	1,332/1,805 (73·8 %)	<0·0001
	Bronchoscopy	236/351 (67·2 %)	1,294/1,805 (71·7 %)	0·0926
	Thorax CT/MRI <u>and</u> bronchoscopy	170/351 (48·4 %)	1,043/1,805 (57·8 %)	0·0012
2018	Thorax CT/MRI	205/341 (60·1 %)	1,369/1,821 (75·2 %)	<0·0001
	Bronchoscopy	238/341 (69·8 %)	1,316/1,821 (72·3 %)	0·3512
	Thorax CT/MRI <u>and</u> bronchoscopy	173/341 (50·7 %)	1,057/1,821 (58·0 %)	0·0123
2019	Thorax CT/MRI	221/331 (66·8 %)	1,382/1,841 (75·1 %)	0·0016
	Bronchoscopy	229/331 (69·2 %)	1,345/1,841 (73·1 %)	0·1463
	Thorax CT/MRI <u>and</u> bronchoscopy	165/331 (49·8 %)	1,085/1,841 (58·9 %)	0·0021

CT, computed tomography; MRI, magnetic resonance imaging; HIV, human immunodeficiency virus

**Supplementary Table 7. Diagnostic procedures by underlying diseases (nationwide)**

Procedure	HIV (n=2124)	Solid malignancies (n=1581)	Hematologic malignancies (n=1865)	Other hematologic diseases (n=158)	Rheumatic/kidney diseases (n=1118)	Pulmonary diseases (n=726)	Gastrointestinal diseases (n=115)	Transplant (n=544)	More than one disease (n=2137)	Not otherwise classified (n=2087)
Thorax CT/MRI	1,307 (61·5%)	1,191 (75·3%)	1,489 (79·8%)	92 (58·2%)	797 (71·3%)	482 (66·4%)	84 (73·0%)	412 (75·7%)	1,676 (78·4%)	1,402 (67·2%)
Bronchoscopy	1,440 (67·8%)	1,096 (69·3%)	1,296 (69·5%)	103 (65·2%)	842 (75·3%)	555 (76·4%)	93 (80·9%)	402 (73·9%)	1,598 (74·8%)	1,469 (70·4%)
Thorax CT/MRI and bronchoscopy	1,013 (47·7%)	877 (55·5%)	1,080 (57·9%)	73 (46·2%)	661 (59·1%)	382 (52·6%)	71 (61·7%)	333 (61·2%)	1,325 (62·0%)	1,104 (52·9%)

CT, computed tomography; MRI, magnetic resonance imaging; HIV, human immunodeficiency virus

**Supplementary Table 8. Inpatient course and complications by underlying diseases (nationwide)**

Event	HIV (n=2,124)	Solid malignancies (n=1,581)	Hematologic malignancies (n=1,865)	Other hematologic diseases (n=158)	Rheumatic/kidney diseases (n=1,118)	Pulmonary diseases (n=726)	Gastrointestinal diseases (n=115)	Transplant (n=544)	More than one disease (n=2,137)	Not otherwise classified (n=2,087)
Death	180 (8·5 %)	639 (40·4 %)	616 (33·0 %)	31 (19·6 %)	309 (27·6 %)	191 (26·3 %)	30 (26·1 %)	102 (18·8 %)	638 (29·9 %)	681 (32·6 %)
ICU care	705 (33·2 %)	693 (43·8 %)	802 (43·0 %)	86 (54·4 %)	585 (52·3 %)	318 (43·8 %)	59 (51·3 %)	258 (47·4 %)	960 (44·9 %)	1,028 (49·3 %)
Mechanical ventilation	574 (27·0 %)	677 (42·8 %)	769 (41·2 %)	75 (47·5 %)	546 (48·8 %)	315 (43·4 %)	60 (52·2 %)	220 (40·4 %)	908 (42·5 %)	998 (47·8 %)
Renal replacement therapy	106 (5·0 %)	100 (6·3 %)	252 (13·5 %)	20 (12·7 %)	195 (17·4 %)	89 (12·3 %)	17 (14·8 %)	220 (40·4 %)	262 (12·3 %)	402 (19·3 %)
Multiple organ dysfunction	422 (19·9 %)	590 (37·3 %)	910 (48·8 %)	76 (48·1 %)	496 (44·4 %)	327 (45·0 %)	60 (52·2 %)	243 (44·7 %)	955 (44·7 %)	944 (45·2 %)
Palliative care	0 (0·0 %)	205 (13·0 %)	62 (3·3 %)	0 (0·0 %)	1 (0·1 %)	7 (1·0 %)	1 (0·9 %)	1 (0·2 %)	94 (4·4 %)	21 (1·0 %)
Cardiac arrest/ Resuscitation	37 (1·7 %)	40 (2·5 %)	88 (4·7 %)	6 (3·8 %)	64 (5·7 %)	43 (5·9 %)	1 (0·9 %)	19 (3·5 %)	75 (3·5 %)	111 (5·3 %)

HIV, human immunodeficiency virus; ICU, intensive care unit

**Supplementary Table 9. Inpatient course and complications by underlying diseases (multi-center study)**

	HIV (n=19)	Solid malignancies (n=7)	Hematologic malignancies (n=9)	Other hematologic diseases (n=2)	Rheumatic/kidney diseases (n=7)	Pulmonary diseases (n=1)	Gastrointestinal diseases (n=1)	Transplant (n=11)	More than one disease (n=8)	Not otherwise classified (n=3)
Deaths	1 (5·3 %)	3 (42·9 %)	2 (22·2 %)	1 (50 %)	1 (14·3 %)	1 (100·0 %)	1 (100·0 %)	0 (0·0 %)	4 (50 %)	1 (33·3 %)
ICU	5 (26·3 %)	1 (14·3 %)	3 (33·3 %)	1 (50 %)	4 (57·1 %)	1 (100·0 %)	1 (100·0 %)	4 (36·4 %)	3 (37·5 %)	2 (66·7 %)
Mechanical ventilation	8 (42·1 %)	5 (71·4 %)	5 (55·6 %)	1 (50 %)	5 (71·4 %)	1 (100·0 %)	1 (100·0 %)	5 (45·5 %)	7 (87·5 %)	3 (100 %)
Renal replacement therapy	1 (5·3 %)	0 (0·0 %)	2 (22·2 %)	0 (0·0 %)	3 (42·9 %)	0 (0·0 %)	1 (100·0 %)	7 (63·6 %)	1 (12·5 %)	2 (66·7 %)
Multiple organ dysfunction	10 (52·6 %)	2 (28·6 %)	4 (44·4 %)	1 (50·0 %)	5 (71·4 %)	1 (100·0 %)	1 (100·0 %)	7 (63·6 %)	7 (87·5 %)	3 (100 %)
Palliative care	1 (5·3 %)	4 (57·1 %)	0 (0·0 %)	0 (0·0 %)	0 (0·0 %)	0 (0·0 %)	0 (0·0 %)	1 (9·1 %)	1 (12·5 %)	0 (0·0 %)
Cardiac arrest/ resuscitation	0 (0·0 %)	0 (0·0 %)	0 (0·0 %)	0 (0·0 %)	0 (0·0 %)	1 (100·0 %)	0 (0·0 %)	0 (0·0 %)	0 (0·0 %)	0 (0·0 %)

HIV, human immunodeficiency virus; ICU, intensive care unit

### **Supplementary references**

1. The database of the German Federal Statistical Office. 2021. <https://www-genesis.destatis.de/genesis/online> (accessed 2 November 2021).